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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,750	02/19/2004	Joseph P. Vacanti	MIT 6917 (CMCC 450) DIV	5014

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EXAMINER	
ISABELLA, DAVID J	
ART UNIT	**PAPER NUMBER**
3738	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)
	10/782,750	VACANTI ET AL.
	Examiner	Art Unit
	DAVID J. ISABELLA	3738

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Status of the Application

The appellant filed an Appeal Brief on 12/8/2006 in response to the final office action mailed on 6/8//2006.

Response to the filing of Appellant's Brief

The finality of the final Office Action has been withdrawn. Upon review of the claims pending on Appeal, the Examiner has applied a new grounds for rejection to the claims as well as maintaining the previous grounds of rejections

Response to Arguments

Applicant's arguments filed 3/13/2006 have been fully considered but they are not persuasive.

Applicant argues that Sparks does not teaçh or suggest that the polymer matrix is seeded with cells. But rather that Sparks relies on natural body processes to produce the necessary connective tissue to the die cavity and form the valve. While it is not entirely clear if Sparks supports applicant's interpretation, examiner maintains Sparks discloses various methods for populating and growing new tissues including seeding, preclotting the matrix with blood and natural induction of tissue growth into the matrix. Beyond Sparks, it was certainly known at the time of applicant's invention to preseed polymer matrix prior to implanting the matrix in the body for growing new tissue. Applicant's attention is directed to Mikos specification, in the background of the invention, Vacanti's teachings for preseeding polymer matrixes prior to implantation to optimize new tissue formation and growth.

Status of the Claims

Claims 1-5,8-17 are currently pending for action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5,8-11,15/1,15/2,15/3,15/4,15/5,15/8,15/9,15/10,15/11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikos (5514378) in view of Sparks (3514791) or Jauregui (4795459).

Claim 1 does not require matrix to be first cultured at a first in vivo site prior to being transplanted to a second site. Therefor, the claim is directed to a method for making a cell-matrix construct comprising implanting into an animal a biodegrable polymer construct in the shape of a heart valve or valve leaflet. The construct having seeded cells therein. The cells may be endothelial, myofibroblast, skeletal muscle, vascular smooth muscle, myocytes, fibromyoblast, and ectoderamal in source.

Mikos discloses every element/step of the claim except for the disclosure of the matrix to be in the form of a heart valve or valve leaflet.

Mikos, column 2, lines 15+, discloses an article by Vacanti, et al (1988) teaching that the scaffold should mimic the natural tissue counterpart. Moreover, Vacanti, et al states that the

scaffold should serve as both a physical support and an adhesive substrate for isolated cells during the culturing thereof.

> Vacanti, et al., "Selective cell transplantation using bioabsorbable artificial polymers as matrices" *J. Pediat. Surg.* 23, 3–9 (1988) and Vacanti, "Beyond Transplantation" *Arch. Surg.* 123, 545–549 (1988), describe an approach for making new organs for transplantation which was not subject to the same limitations as the work of Yannas and Burke, i.e., it was not limited to the construction of very thin organs such as skin. Vacanti, et al., recognized that cells require a matrix for attachment and support if they are to survive following implantation, that a minimum number of cells was essential for function in vivo, and that the matrix must be porous enough to allow nutrients and gases to reach all of the cells on and within the matrix by diffusion, until the matrix-cell structure was vascularized. Moreover, they recognized the advantage of using synthetic biodegradable polymer substrates to form a scaffold that mimics its natural counterparts, the extracellular matrices (ECM) of the body, serving as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture, and subsequent implantation, degrading as the cells begin to secrete they own ECM support. Subsequent studies have demonstrated that even better results are obtained when the matrix is first implanted, prevascularized, and then seeded with cells. Most matrices used in the earlier work are modifications of materials already available, such as surgical sutures and meshes. This latter approach, however, requires new matrix configurations which are optimal for vascularization, yet resistant to compression, with sufficient porosity and interconnected interstitial spacings to allow injected cells to become dispersed throughout the matrix.

Furthermore, Mikos is specific as to the purpose of tailoring the bioabsorbable matrix according to the selected biological tissue to be grown. See column 13, lines 31+.

> The matrix scaffold is used to mimic its natural counterparts, the extracellular matrices (ECM) of the body. It serves as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture and subsequent implantation. As the transplanted cell population grows and the cells function normally, they begin to secrete their own ECM support. Concurrently, when using a biodegradable matrix material, the scaffold continuously degrades and is eliminated as the need for an artificial support diminishes. In the reconstruction of structural tissues like cartilage and bone, tissue shape is integral to function. Therefore, these scaffolds must be processable into devices of varying thickness and shape.
>
> Preparation of Anatomical Shapes
>
> The membranes are processed into anatomical shapes, or foams, for use in reconstructive surgery or organ transplantation, as depicted in FIG. 3 (described in more detail

Moreover, Mikos teaches that various cells types may be used for culturing new tissues. See column 14, lines 25+.

> Use of the Matrix for Reconstructive Surgery
>
> The three-dimensional structure is specifically designed to provide a matrix for dissociated cells such as chondrocytes or hepatocytes to create a three-dimensional tissue or organ. Any type of cell can be added to the matrix for culturing and possible implantation, including cells of the muscular and skeletal systems, such as chondrocytes, fibroblasts, muscle cells and osteocytes, parenchymal cells such as hepatocytes, pancreatic cells (including Islet cells), cells of intestinal origin, and other cells such as nerve cells and skin cells, either as obtained from donors, from established cell culture lines, or even before or after genetic engineering. Pieces of tissue can also be used, which may provide a number of different cells types in the same structure.
>
> The cells are obtained from a suitable donor or the patient into which they are to be implanted, dissociated using standard techniques, and seeded onto and into the matrix. These are optionally cultured in vitro prior to implantation. Alternatively, the matrix is implanted, allowed to vascularize, then the cells injected into the matrix. Methods and reagents for culturing cells in vitro and implantation of a matrix are known to those skilled in the art.

Each of Jauregui and Sparks teaches the seeding of a scaffold with tissues/cells for growing heart valve/leaflets. While Mikos is silent to growing of vascular tissues, the use of tissue engineering employing both bioresorbable and nonresorbable polymer scaffolds to replace diseased, defective or injured tissues, including vascular tissues, is known in the art as taught by Jauregui and Sparks. To use the method of Mikos in producing a vascular tissue equivalent with the use as a bioresorbable scaffold that is seeded with tissues/cells would have been obvious to one with ordinary skill in the art from the teachings of either of Jauregui or Sparks.

Claim 2, see column 14, lines 25+ of Mikos.

Claim 3, see method of Sparks. Sparks teaches culturing a tissue replacement in vivo at a first site and removing the tissue replacement and transplanting the tissue replacement at a second site.

Claim 4, see teachings of Jauregui or Sparks for forming a scaffold in the form of a heart valve or valve leaftlet .

Claim 5, see column 14, lines 25 of Mikos.

Claim 8, since the tissue equivalent of Jauregui and Sparks are used to replace similar in vivo tissue, the tissue equivalent would inherently possess the require physical characteristics to perform the intended replacement function.

Claims 9 and 10, see column 3, lines 5+ of Mikos.

Claim 11, see graphs 2A&B of Mikos.

Claims 12-14,15/12,15/13,15/14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikos (5514378) in view of Sparks (3514791) or Jauregui (4795459) further in view of Griffith-Cima et al (5709854).

The use of growth factors in combination with seeding of cells on a scaffold to promote cellular attachment and differentiation would have been obvious to one with ordinary skill in the art from the teachings of Griffith-Cima.

The polymeric matrix can be combined with humoral factors to promote cell transplantation and engraftment. For example, the polymeric matrix can be combined with angiogenic factors, antibiotics, antiinflammatories, growth factors, compounds which induce differentiation, and other factors which are known to those skilled in the art of cell culture.

For example, humoral factors could be mixed in a slow-release form with the cell-alginate suspension prior to formation of implant or transplantation. Alternatively, the hydrogel could be modified to bind humoral factors or signal recognition sequences prior to combination with isolated cell suspension.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5,8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sparks (3514791) in view of Mikos (5514378) or Griffith-Cima et al (5709854) and in view of the teachings of either of Jauregui (4795459) or Tang et al (4916193).

Sparks discloses a method for making a cell-matrix construct for use as a heart valve comprising implanting into an animal a fibrous matrix formed of a polymer that has been seeded with specific selected cells. See column 5,lines 5-75 for specific disclosure directed to the method for forming any of a tricuspid, bicuspid or individual valve leaflets.

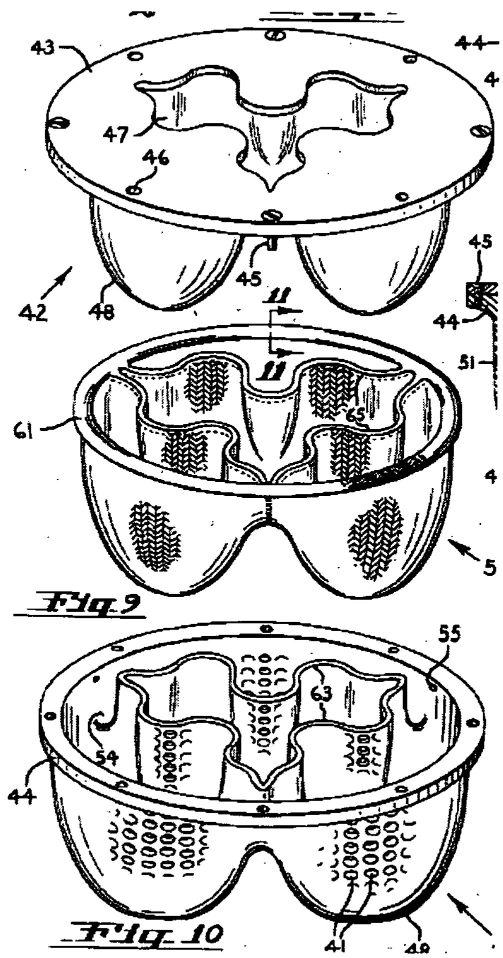

Fig. 9

Fig. 10

Sparks fails to teach that the matrix is biodegradable. Mikos and Griffith-Cima et al teach the use of biodegradable matrix which is designed to allow biological tissue ingrowth to form a structure before the matrix is completely bioabsorbed.

Mikos, column 2, lines 15+, discloses an article by Vacanti, et al (1988) teaching that the scaffold should mimic the natural tissue counterpart. Moreover, Vacanti, et al provides evidence that better results are obtained when the matrix is first implanted, prevascularized and then seeded with select cells.

> Vacanti, et al., "Selective cell transplantation using bioabsorbable artificial polymers as matrices" *J. Pediat. Surg.* 23, 3–9 (1988) and Vacanti, "Beyond Transplantation" *Arch. Surg.* 123, 545–549 (1988), describe an approach for making new organs for transplantation which was not subject to the same limitations as the work of Yannas and Burke, i.e., it was not limited to the construction of very thin organs such as skin. Vacanti, et al., recognized that cells require a matrix for attachment and support if they are to survive following implantation, that a minimum number of cells was essential for function in vivo, and that the matrix must be porous enough to allow nutrients and gases to reach all of the cells on and within the matrix by diffusion, until the matrix-cell structure was vascularized. Moreover, they recognized the advantage of using synthetic biodegradable polymer substrates to form a scaffold that mimics its natural counterparts, the extracellular matrices (ECM) of the body, serving as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture, and subsequent implantation, degrading as the cells begin to secrete they own ECM support. Subsequent studies have demonstrated that even better results are obtained when the matrix is first implanted, prevascularized, and then seeded with cells. Most matrices used in the earlier work are modifications of materials already available, such as surgical sutures and meshes. This latter approach, however, requires new matrix configurations which are optimal for vascularization, yet resistant to compression, with sufficient porosity and interconnected interstitial spacings to allow injected cells to become dispersed throughout the matrix.

Furthermore, Mikos is specific as to the purpose of tailoring the bioabsorbable matrix according to the selected biological tissue to be grown. See column 13, lines 31+.

> The matrix scaffold is used to mimic its natural counterparts, the extracellular matrices (ECM) of the body. It serves as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture and subsequent implantation. As the transplanted cell population grows and the cells function normally, they begin to secrete their own ECM support. Concurrently, when using a biodegradable matrix material, the scaffold continuously degrades and is eliminated as the need for an artificial support diminishes. In the reconstruction of structural tissues like cartilage and bone, tissue shape is integral to function. Therefore, these scaffolds must be processable into devices of varying thickness and shape.
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Moreover, Mikos teaches that various cells types may be used for culturing new tissues. See column 14, lines 25+.

Use of the Matrix for Reconstructive Surgery

The three-dimensional structure is specifically designed to provide a matrix for dissociated cells such as chondrocytes or hepatocytes to create a three-dimensional tissue or organ. Any type of cell can be added to the matrix for culturing and possible implantation, including cells of the muscular and skeletal systems, such as chondrocytes, fibroblasts, muscle cells and osteocytes, parenchymal cells such as hepatocytes, pancreatic cells (including Islet cells), cells of intestinal origin, and other cells such as nerve cells and skin cells, either as obtained from donors, from established cell culture lines, or even before or after genetic engineering. Pieces of tissue can also be used, which may provide a number of different cells types in the same structure.

The cells are obtained from a suitable donor or the patient into which they are to be implanted, dissociated using standard techniques, and seeded onto and into the matrix. These are optionally cultured in vitro prior to implantation. Alternatively, the matrix is implanted, allowed to vascularize, then the cells injected into the matrix. Methods and reagents for culturing cells in vitro and implantation of a matrix are known to those skilled in the art.

Griffith-Cima teaches that the degradable template may be shaped or formed prior to implantation into the patient.

the hydrogel. However, the matrix may also be molded and implanted in one or more different areas of the body to suit a particular application. This application is particularly relevant where a specific structural design is desired or where the area into which the cells are to be implanted lacks specific structure or support to facilitate growth and proliferation of the cells.

The site, or sites, where cells are to be implanted is determined based on individual need, as is the requisite number of cells. For cells having organ function, for example, hepatocytes or islet cells, the mixture can be injected into the mesentery, subcutaneous tissue, retroperitoneum, properitoneal space, and intramuscular space. For formation of cartilage, the cells are injected into the site where cartilage formation is desired. One could also apply an external mold to shape the injected solution. Additionally, by controlling the rate of polymerization, it is possible to mold the cell-hydrogel injected implant like one would mold clay.

Alternatively, the mixture can be injected into a mold, the hydrogel allowed to harden, then the material implanted.

Each of Jauregui and Tang et al teaches the doctrine of equivalence between resorbable and non resorbable materials as used in heart valve applications similar to that as disclosed in column 4 of applicants specification. To replace the non-absorbable mesh of Sparks with an absorbable matrix as taught by Mikos or Griffith-Cima et al to allow for a degradable template

for new tissue formation would have been obvious to one with ordinary skill in the art especially in light of the Vacanti publication (as disclosed in Mikos) which teaches the benefits of selected cells transplantation on bioabsorbable polymer matrix.

Applicant specification fails to teach and/or disclose any unobvious benefits or criticalities in the selection of the materials used for the seeding of the cells. Accordingly, examiner maintains that the materials used are well known in the art and are, in many instances, known equivalents as taught by Jauregui or Tang et al. It should be evident that at the time of Sparks invention (1967) the use of resorbable material in tissue applications was in its infancy. At the time of applicant's invention (2004), great strides have been made in the prosthetic art in replacing non-resorbable materials with resorbable materials for various known benefits. The use of resorbable material as the substrate for seeding cells to form a tissue construct would have been obvious to one with ordinary skill in the art from the teachings of any of the secondary references. With respect to the limitation of "withstand repeated stress and strain", the device of Sparks as modified would inherently possess the properties that would be capable of withstanding cyclic stresses and strains since the valve is designed to function as a replacement of a natural existing valve.

Claim 2, see cells disclosed by Sparks.

Claim 3, Sparks discloses the steps of culturing a matrix at a first site then transplanting the new tissue to a desired site.

Claim 4, one embodiment disclosed by Sparks is a heart valve.

Claim 5, see cells of sparks or Schmidt, et al.

Claim 8, the newly formed heart tissue of Sparks would inherently possess the strength, flexibility and/or pliability of the tissue it is to replace.

Claims 9 and 10, see materials disclosed by Mikos or Griffith-Cima et al.

Claim 11, see Mikos.

Claims 12-14, see Mikos or Griffith-Cima et al.

Claim 15, see construct of Sparks as modified by either of Mikos or Griffith-Cima et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID J. ISABELLA whose telephone number is 571-272-4749. The examiner can normally be reached on MONDAY-FRIDAY.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CORRINE MCDERMOTT can be reached on 571-272-4754. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID J ISABELLA
Primary Examiner
Art Unit 3738

DJI
5/25/2006